#8 UM 4/15/93

91-318

UNITED STATES PATENT AND TRADEMARK OFFICE

Examiner: J. Spear Art Unit: 1502

Re: Application of: Benjamin OSHLACK, et al.

Serial No.: 07/800,549

Filed: November 27, 1991

For: CONTROLLED RELEASE OXYCODONE COMPOSITIONS

DECLARATION OF DR. ROBERT FRANCIS KAIKO

Dr. Robert Francis Kaiko declares as follows:

1. My full name is Robert Francis Kaiko. I reside at 450 Norfield Woods Road, Weston, Connecticut, U.S.A. 06883.

2. I am currently Vice-President, Clinical Research for the Purdue Frederick Company, Norwalk, Connecticut, U.S.A., where, among other duties, I am responsible for supervising project leaders regarding the planning, conducting and reporting of clinical research activities involving analgesic drugs.

3. As can be ascertained from my attached Curriculum Vitae, I received a Bachelors of Science Degree in Pharmacy from the University of Connecticut in 1970 and a Doctorate in Pharmacology from the Cornell University Graduate School of Medical Sciences in New York in 1974. Thereafter, I undertook a Post-Doctoral Research Fellowship at the Cornell University Medical College, Department of Pharmacology during the years 1975-1976.

4. Between 1974 and 1985, I held research and academic appointments in the Analgesic Studies Section of the Memorial Sloan-Kettering Cancer Center, as well as the Department of Pharmacology, Cornell University Medical College. Within the Analgesic Studies Section, I initially established a clinical pharmacokinetics laboratory and subsequently took considerable responsibility for the conduct and reporting of the evaluation of

a wide variety of analgesics in cancer patients. My primary responsibility at Cornell University Medical College was the education of medical students in the clinical pharmacology of opioid analgesics.

5. I have been active in numerous scientific and medical societies and I served as President of the Eastern Pain Association in 1988-1989. Currently, I am on the Board of Directors of the Eastern Pain Association. I have also served more than five years on the American Society for Clinical Pharmacology and Therapeutics Analgesiology Sections Committee on the (US) FDA Guidelines for the Clinical Evaluation of Analgesic Drugs. I have also served as a consultant to the Food and Drug Administration, the Drug Abuse Advisory Board, the World Health Organization, the National Cancer Institute, and the National Institute on Aging. I am often called upon to participate in regional, national, and international scientific and medical education and research forums.

6. I am also a peer reviewer for several journals. More particularly, I have been a Board Member of Pain and Analgesia, PRN Forum, Contributing Editor of Journal of Pain and Symptom Management, Cancer Pain Release, and a reviewer for Journal of Pharmaceutical Sciences, Pharmacotherapy, Drugs, Drug Bulletin, American Journal of Medicine.

7. I have authored more than 75 reviewed articles and more than 115 abstracts, most of which relate to the clinical pharmacology of a wide variety of analgesic medications.

8. Many of my publications are directed to the pharmacologic effects of opioid analgesics in humans, and over 50 of my publications are directed to the results of clinical studies concerning morphine in various formulations. These articles address various aspects of the pharmacokinetics and pharmacodynamics of morphine in humans, e.g., plasma concentrations of morphine, the analgesic

effects of morphine, including the length of analgesia obtained by the various formulations tested in these clinical studies.

9. I believe that my experience as detailed above and in my attached curriculum vitae establishes me as an expert in the pharmacology of opioid analgesics. The discipline of pharmacology encompasses pharmacokinetics which deals with the rates of movement of a drug or its metabolites into the body, among its many compartments, and out of the body (i.e., the absorption, distribution, biotransformation, and excretion of drugs); and pharmacodynamics which deals with the biochemical and physiological effects of drugs and their mechanisms of action. Operationally, pharmacokinetics may be defined as what the body does to the drug, and pharmacodynamics may be defined as what the drug does to the body.

10. I have reviewed and am familiar with the subject matter and claims of U.S. Patent Application Serial No. 07/800,549, filed November 27, 1991, entitled "CONTROLLED RELEASE OXYCODONE COMPOSITIONS". I have also reviewed U.S. Patent No. 4,990,341 (hereinafter referred to as "the Goldie, et al. '341 patent"), U.S. Patent No. 4,861,598 (hereinafter referred to as "the Oshlack '598 patent"), the combination of which I am informed forms the basis of the Examiner's rejection of the claims based on obviousness.

a. I am aware that the Goldie, et al. '341 patent has been relied upon as teaching a controlled-release matrix formulation for hydromorphone which shows peak plasma levels attained between 2.25 and 3.75 hours, whereas the Oshlack '598 patent has been cited for teaching matrix compositions as those in the present patent application wherein the active agent is oxycodone. I am further aware that the Examiner has taken the position that it would have been obvious to one of ordinary skill in the art to use oxycodone in the Goldie, et al. '341 patent.

b. The claims of the present patent application are all related in part to the fact that in order to have at least a 12 hour duration of therapeutic activity, the time to reach peak plasma level (t_{max}) of oxycodone in an oral controlled-release formulation should be from 2 to 4 hours after administration. The inventors have further characterized the invention in the claims by way of in vitro release rate, pH and other characteristics.

11. It is my opinion that one skilled in the art having information concerning the time to reach peak plasma concentration (hereinafter referred to as "the t_{max}") and duration of effect for a controlled-release hydromorphone formulation as set forth in the Goldie, et al. '341 patent, could not predict whether a controlled-release oxycodone formulation having a t_{max} in 2-4 hours would also provide a duration of therapeutic effect of at least 12 hours.

a. It is my further opinion that the teaching of a controlled-release matrix formulation of oxycodone with accompanying in vitro dissolution data is not predictive of the t_{max} and the duration of effect which would be achieved with such a formulation in vivo.

12. One cannot infer that in vitro release characteristics of a formulation for a particular drug giving rise to certain in vivo peak plasma levels and duration of activity (in this case, hydromorphone as taught in the Goldie, et al. '341 patent) will provide the same duration of activity for another drug (i.e., oxycodone).

13. The unpredictable correlation between the pharmacokinetics and pharmacodynamics (referred to in the art as "PK/PD") of a formulation is a basic tenet of pharmacology.

14. The relationship between the pharmacokinetics and pharmacodynamics of opioid analgesics is particularly complex and unpredictable because of many confounding factors. Opioid receptors occupy peripheral pharmacokinetic compartments rather than the

central compartment from which plasma concentrations are sampled, leading to a lag time or disequilibrium between the time-course of plasma opioid levels and the time-action of the opioid. Mathematical modeling has attempted to deal with this disequilibrium, but the results are not predictive among different patients. In addition, different opioid effects are mediated by opioid receptors that are not part of the same pharmacokinetic compartment, but rather are parts of different peripheral pharmacokinetic compartments.

15. Extensive clinical studies are required before regulatory approval of even a close derivative of a well-known drug (e.g., by the (U.S.) FDA).

16. In my publication entitled "Relationships Between Opioid Disposition and Their Pharmacological Effects - An Overview", Postgrad. Med. J., 67 (suppl. 2), 544-549 (1991), which is an overview of opioid pharmacokinetics and their effects, I stated:

> The understanding of the metabolic disposition and pharmacokinetics of opioid analgesics and their relationship to therapeutic and adverse effects ... has provided the beginning of an applied science in this area. Given the experimental nature and complexity of pharmacokinetic/pharmacodynamic relationships and the state of the art in this area, the most meaningful therapeutic conclusions and extrapolations remain those based on the results of the most adequate and well-controlled therapeutic evaluations..."

A copy of my publication is attached as Exhibit 1.

17. With regard to the Oshlack '598 patent, in vitro dissolution data are but one of many factors which must be considered when formulating a particular drug composition, and are often not indicative of in vivo effect. One skilled in the art would not be able to accurately predict whether an oxycodone formulation with

the in vitro dissolution taught in the Oshlack '598 patent would provide the pharmacokinetics (including the t_{max}) and the pharmacodynamics (including the duration of effect) set forth in the claims of the presently considered patent application identified above.

18. It is therefore my opinion that one skilled in the art would not arrive at the presently claimed invention by combining the teachings of the Goldie, et al. '341 patent with the Oshlack '598 patent.

19. The declarant further states that the above statements were made with the knowledge that willful false statements and the like are punishable by fine and/or imprisonment, or both, under §1001 of Title 18 of the United States Code, and that any such willful false statement may jeopardize the validity of this application or any patent resulting therefrom.

Date: 3/9/93

Dr. Robert Francis Kaiko

W\PF10\RK-DEC.318

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Robert Francis Kaiko, Ph.D.
Weston, CT
USA

INVENTORS BACKGROUND (see attached Curriculum Vitae)

Education:

This inventor received a Bachelors of Science degree in pharmacy from the University of Connecticut in 1970 and a Doctorate in Pharmacology from the Cornell University Graduate School of Medical Sciences in New York in 1974. This was followed by a postdoctoral research fellowship at the Cornell University Medical College, Department of Pharmacology during 1975 and 1976.

Research and Academic Appointments:

Between 1974 and 1985 the inventor held research and academic appointments in the Analgesic Studies Section of the Memorial Sloan-Kettering Cancer Center, as well as the Department of Pharmacology, Cornell University Medical College. Within the Analgesic Studies Section, Dr. Kaiko initially established a clinical pharmacokinetics laboratory and subsequently took considerable responsibility for the conduct and reporting of the evaluation of a wide variety of analgesics in cancer patients. The primary responsibility at Cornell University Medical College was the education of medical students in the clinical pharmacology of opioid analgesics.

Extramural Activities:

Dr. Kaiko has been active in numerous scientific and medical societies and served as President of the Eastern Pain Association in 1988 and 1989. The inventor is currently on the Board of Directors of the Eastern Pain Association. For more than five years the inventor has served on the American Society for Clinical Pharmacology and Therapeutics Analgesiology Sections Committee on the FDA Guidelines for the Clinical Evaluation of Analgesic Drugs. The inventor has served as a consultant to the Food and Drug Administration, The Drug Abuse Advisory Board, The Federal Trade Commission, World Health Organization, The National Cancer Institute and The National Institute on Aging, as well as a peer reviewer for several journals.

Bibliography:

The inventor has authored more than 75 peer-reviewed articles and more than 115 abstracts, most of which relate to the clinical pharmacology of a wide variety of analgesic medications.

Pharmaceutical Industry Appointments:

In 1985 the inventor joined The Purdue Frederick Company as Associate Medical Director and subsequently was promoted to Associate Medical Director, Senior Director, Clinical Research followed by Medical Director, Clinical Research and now, Vice President, Clinical Research. While currently the inventor is responsible for considerable administrative duties within the Medical Department of The Purdue Frederick Company, he supervises project leaders primarily responsible for the planning, conduct, and reporting of clinical research activities involving analgesic drugs and also supervises biostatistical and clinical data management operations. In addition, the inventor is commonly called upon to participate in numerous regional, national, and international scientific and medical education and research forums.

Background of Invention:

In the management of pain with opioid analgesics, it has been commonly observed and reported that there is considerable inter-individual variation in the response to a given dose of a given drug and, therefore, considerable variability among patients in the dosage of opioid analgesic required to control pain without unacceptable side effects. This necessitates considerable effort on the part of clinicians in establishing the appropriate dose in an individual patient through the time consuming process of titration, which requires careful assessment of both therapeutic and side effects and dosage adjustments over a period of days and sometimes longer before the appropriate dosage is determined. The American Pain Society's 3rd Edition of Principles of Analgesic Use in the Treatment of Acute Pain and Cancer Pain explains that one should "be aware that the optimal analgesic dose varies widely among patients. Studies have shown that in all age groups, there is enormous variability in doses of opioids required to provide relief, even among opioid naive patients with identical surgical lesions.... This great variability underscores the need to write analgesic orders that include provision for supplementary doses, and to use intravenous boluses and infusions to provide rapid relief of severe pain.... Give each analgesic an adequate trial by dose titration.... before switching to another drug."

Surveys of daily dosages of opioid analgesics required to control pain suggest that an approximately eight-fold range in daily dosages is required to control pain in approximately 90% of patients. This extraordinary wide range in the appropriate dosage makes the titration process particularly time consuming and resource consuming, as well as leaving the patient without acceptable pain control for an unacceptably long duration.

An opioid analgesic treatment which acceptably controls pain over a substantially narrower daily dosage range will substantially improve the efficiency and quality of pain management.

INVENTION

Acrogesic (Oxycodone Acrocontin) acceptably controls pain over a substantially narrower, approximately four-fold (10 to 40 mg q12h around-the-clock dosing) in approximately 90% of patients. This is in sharp contrast to the approximately eight-fold range required for approximately 90% of patients for opioid analgesics in general. Morphine is the prototypic opioid analgesic and, as with Acrogesic, has been formulated into a q12h controlled-release formulation. Regardless of the fact that both controlled-release oxycodone and control release morphine administered q12h around-the-clock possess qualitatively comparable clinical pharmacokenitic characteristics, Acrogesic can be used over approximately 1/2 the dosage range as MS Contin to control 90% of patients with significant pain.

Clinical Pharmacokinetics:

Single dose pharmacokinetic studies of Acrogesic in comparison to immediate release oral oxycodone demonstrates comparable extents of absorption but a slower rate of absorption with Acrogesic resulting in a maximal plasma oxycodone concentration approximately half that obtained with the immediate release product at the same administered dose. Similar single dose studies with MS Contin and immediate release oral morphine provide for comparable relative results.

Repeated dose studies with Acrogesic administered q12h in comparison with immediate release oral oxycodone administered q6h at the same total daily dose result in comparable extents of absorption, as well as comparable maximum and minimum concentrations with the time of maximum concentration approximately 3 hours with the controlled-release product as compared to approximately 1 hour with the immediate release product. Similar repeated dose studies with MS Contin as compared to immediate release morphine provide for comparable relative results as with Acrogesic.

Analgesic Efficacy and Dose Response Relationships

While some may suggest that differences in the magnitude of the dosage range required to control pain in a comparable percentage of patients could be explained on the basis of substantial differences in the slopes of the dose-response curves for two different treatments, a detailed examination of the literature reveals no substantial deviation from parallelism of the dose response curves for oxycodone either in the forms of Acrogesic, immediate release oral oxycodone or parenteral oxycodone in comparison with oral and parenteral opioids with which oxycodone has been compared in terms of dose-response studies and relative analgesic potency assays.

Beaver and associates reported comparable dose-response slopes for parenteral oxycodone as compared to parenteral morphine and comparable dose-response slopes for oral as compared to parenteral oxycodone. Sunshine and associates demonstrated a significant dose-response relationship utilizing Acrogesic dosages of 10, 20 and 30 mg which does not deviate from parallelism with dose-response slopes for MS Contin in similarly designed well-controlled analgesic efficacy studies of MS Contin reported by Van Wagoner who compared 30, 60, 90,

and 120 mg of MS Contin as compared with 10 mg of intramuscular morphine and placebo and Bloomfield who compared 30 and 90 mg of MS Contin as compared to 30 and 90 mg of another controlled-release oral morphine preparation, Oramorph SR 30 mg tablets.

A review of dose-response studies and relative analgesic assays of mu-agonist opioid analgesics, which include oxycodone, morphine, hydromorphone, levorphanol, methadone, meperidine, heroin, all indicate no significant deviation from parallelism in their dose response relationships. This is so well established that it has become an underlining principal providing for establishing relative analgesic potency factors and dose ratios which are commonly utilized when converting patients from one mu-agonist analgesic to another regardless of the dosage of the former. Unless the dose response curves are parallel, conversion factors would not be valid across the wide range of dosages involved when substituting one drug for another.

CLINICAL SIGNIFICANCE

The clinical significance provided by Acrogesic at a dosage range of 10 to 40 mg q12h for acceptable pain management in approximately 90% of patients with moderate to severe pain as compared to other opioid analgesics, requiring approximately twice the dosage range provides for the most efficient and humane method of managing pain requiring repeated dosing. The expertise and time of physicians and nurses, as well as the duration of unacceptable pain patients must endure during the opioid analgesic titration process is substantially reduced through the efficiency of Acrogesic usage.

Curriculum Vitae

Robert Francis Kaiko

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10 Norfield Woods Road
Weston, CT 06883
(203) 454-0107

Personal Information:

Birthdate:	1/5/47
Birthplace:	Norwich, Connecticut
Marital Status:	Married - Lucy Li
Children:	Three sons, one daughter

Education:

1970	B.S.	University of Connecticut Storrs, CT (Pharmacy)
1974	Ph.D.	Cornell University Graduate School of Medical Sciences New York, New York (Pharmacology)

Research and Academic Appointments:

1990 - Present	Vice President, Clinical Research The Purdue Frederick Company Norwalk, Connecticut
1988 - 1990	Medical Director, Clinical Research The Purdue Frederick Company Norwalk, Connecticut
1987 - 1988	Associate Medical Director, Senior Director, Clinical Research The Purdue Frederick Company Norwalk, Connecticut

Research and Academic Appointments (continued):

1985 - 1987	**Associate Medical Director** The Purdue Frederick Company Norwalk, Connecticut
1984 - 1985	**Assistant Member** Memorial Sloan-Kettering Cancer New York, New York
1982 - 1985	**Assistant Member** Sloan-Kettering Institute, Analgesic Studies Section New York, New York
1980 - 1982	**Associate** Sloan-Kettering Institute, Analgesic Studies Section New York, New York .
1979 - 1985	**Adjunct Assistant Professor** Cornell University Graduate School of Medical Sciences, Dept. of Pharmacology New York, New York
1979 - 1985	**Instructor** Cornell University Medical College, Department of Pharmacology New York, NY
1975 - 1976	**Postdoctoral Research Fellow** Cornell University Medical College, Department of Pharmacology New York, NY
1974 - 1980	**Research Associate** Sloan-Kettering Institute for Cancer Research, Analgesic Studies Section New York, NY

Scientific and Medical Societies

Eastern Pain Association
- Scientific Program Chairman, E.P.A., 1984
- Regional Delegate, 1983 - 1985
- Vice President, 1987
- President, 1988 and 1989

International Narcotics Research Conference
American Pain Society
American Federation for Clinical Research
New York Academy of Sciences
American Society of Pharmacology and Experimental Therapeutics
American Society for Clinical Pharmacology and Therapeutics
- Analgesiology Section's Committee on the FDA Guidelines for Clinical Evaluation of Analgesic Drugs, 1986 - 1987

International Association for the Study of Pain
American College of Clinical Pharmacology

Journals and Publications

Board Member Pain and Analgesia, PRN Forum
Contributing Editor Journal of Pain and Symptom Management, Cancer Pain Release
Reviewer Journal of Pharmaceutical Sciences, Pharmacotherapy, Drugs, Drug Bulletin, American Journal of Nursing

Consultant

Food and Drug Administration; Drug Abuse Advisory Board; Federal Trade Commission; World Health Organization; pharmaceutical industry

Grant Reviewer/Site Visitor

National Cancer Institute; Veterans Administration.

Research Support

National Cancer Institute; National Institute on Drug Abuse; National Institute on Aging; pharmaceutical industry

Community Service

Chair, Cornell Fund for Underprivileged Children Task Force
Trustee, Central Presbyterian Church

Prizes and Awards

Pharmacology Prize, University of Connecticut, 1970
NIH PredoctoralTrainee, 1970-1974

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